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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,553	04/24/2001	Hikaru Takakura	TAKAKURA=1A	4153

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	7

DATE MAILED: 01/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,553	TAKAKURA ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,7,9 and 10* is/are rejected.

7)☒ Claim(s) *3 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/894,818* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-10 are still at issue and are present for examination. Claims 2-5, 7-10 are now under consideration. Claims 1 and 6 remain withdrawn from consideration as they are drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 2-5, 7-10 in Paper No. 5 is acknowledged. Examiner regrets the inadvertent error in classifying claim 1 drawn to polypeptide in group I. As applicants have claimed polynucleotides in group I, Examiner has reclassified claim 1 in group II and examined all claims directed to polynucleotides in Group I.

The traversal of the rejection is on the ground(s) that coexamination of all of Groups I-II would not a burden on the Examiner. This is not found persuasive because while the searches for the two groups overlap, they are not coextensive and constitute independent and distinct inventions as explained n the previous Office action. The search for Groups I and II would each require the search of subclasses unnecessary for the search of elected Group I. Furthermore, the search involves an extensive search of the non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1 and 6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 5.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 08/894,818, filed on 5-20-1998.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that figures and figure descriptions as well as specification text (for example page 51) lacks SEQ ID NO for any amino acid sequence comprising four or more amino acids and any nucleotide sequence comprising ten or more nucleotides. See particularly 37 CFR 1.821(d).

Claim Objections

Claims 2 and 7 are objected to because of the following informalities: Claims 2 and 7 depend from claims 1 and 6 respectively which are non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the phrase "gene according to claim 2". It is not clear to the Examiner as to what applicants mean by the term "gene" in the present context while referring to claim 2. This is because it is well understood in the art the term gene encompasses the nucleotide sequences other than those encoding the polypeptide such as regulatory sequences. However, claim 2 is simply drawn to a polynucleotide encoding the hyperthermostable protease. Therefore it is not clear to the Examiner whether the term "gene" simply refers to the polynucleotide sequences encoding the polypeptide or comprises more than that. Simply replacing the term "gene " with "polynucleotide' would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4-5 and 7, 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA with SEQ ID NO:2 or 6 encoding a polypeptide with SEQ ID NO:1 or 5 respectively, having hyperthermostable protease activity, does not reasonably provide enablement for any or all DNA encoding any or all hyperthermostable proteases or any DNA that can hybridize to either SEQ ID NO:2 or 6 or any DNA encoding a

functional equivalents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2, 4-5 and 7, 9-10 are so broad as to encompass any or all DNA which encodes any or all hyperthermostable proteases and vectors and host cells comprising such DNAs. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences that are broadly encompassed by the claims.

The applicants propose to use the above polynucleotides for a variety of processes including recombinant protein preparation. Since the nucleotide sequence determines the type of protein and the ultimate function of the encoded protein, changing the nucleotide sequences as proposed by the applicants and/or addition of substantial amount of additional nucleotide sequence unrelated to the nucleic acid sequence of SEQ ID NO:2 or 6 may not lead to desired function of the polynucleotides. This is because the changes suggested by the applicants will result in an enormous number of nucleotide sequences that will hybridize to several unrelated mRNAs instead of hybridizing specifically to mRNA of interest and similarly may hybridize to

cDNAs totally unrelated to cDNA of interest while screening a cDNA library and may not encode the protein of interest. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of just two hyperthermostable proteases isolated from a single source.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA encoding a protein having hyperthermostable protease activity because the specification does not establish: (A) a rational and predictable scheme for isolation and characterization of polynucleotides encoding a hyperthermostable protease from any or all sources; (B)regions of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (C) the general tolerance of hyperthermostable protease DNA sequence to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any nucleotide in the polynucleotide encoding a hyperthermostable protease with an expectation of obtaining the desired biological function and utility; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all DNA encoding hyperthermostable protease. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 2, 4-5 and 7, 9-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules encoding a hyperthermostable protease or a genus of DNA molecules capable of hybridizing to the polynucleotides encoding polypeptides with SEQ ID NO:1 or 5 or their functional equivalents.

The specification does not contain any disclosure of the structure of all DNA sequences claimed. The genus of cDNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species

within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4-5, and 7, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klingeberg et al.(Appl. Microbiol. Biotechnol., 1991, Vol. 34:715-719) and the common knowledge in the art of molecular biology to clone a purified protein (provided by several Molecular biology laboratory manuals). Claims 2, 4-5, and 7, 9-10 in this instant application are drawn to an isolated polynucleotide encoding a hyperthermostable protease or functional equivalent thereof wherein the DNA can hybridize to the polynucleotide with SEQ ID NO:2 or 6 and a method of making the protease by culturing a transformant transformed with the above polynucleotides followed by culturing and harvesting the recombinant protein.

The reference of Klingeberg et al. discloses the isolation, purification and characterization of hyperthermostable proteases from five archaeobacterial sources. However, the reference does not teach the polynucleotide encoding such proteases or a method of making the proteases using

the transformed host cells. The reference also does not teach whether the polynucleotides of those proteases hybridizes to the polynucleotide with SEQ ID NO:2 or 6.

Using the purified enzymes taught by Klingeberg et al. it would have been obvious to one of ordinary skill in the art to make the polynucleotide encoding the same and to make the recombinant form of the same using the common knowledge of cloning available in the art of molecular biology. It is common knowledge in the art that the cDNA encoding the purified proteins and the recombinant proteins of a purified protein can be made by obtaining the amino acid sequence of a small portion of the purified protein followed by making oligonucleotide probes and synthesizing cDNA clones using a cDNA library. Once a full length cDNA clone becomes available, it is to be subcloned into expression vector followed by transforming a host cell. Culturing such transformed host cells under conditions ideal for expression of the heterologous polypeptide yields recombinant form of the purified protein. Several commercial kits are available in the art to perform such experiments including several commercial cDNA libraries. One of ordinary skill in the art would have been motivated to make the polynucleotide encoding the protease and the recombinant form of the above protein for either making the protein in larger amounts, or for studying the molecular structure of the enzyme or simply to study the enzyme kinetics in more detail. One of ordinary skill in the art would have a reasonable expectation of success since Klingeberg et al. provide the purified protein and the art provides the techniques for making the polynucleotide encoding the same and the recombinant form of the above protein. Furthermore, because the polynucleotide made using the teachings of Klingeberg et al. encodes a hyperthermostable protease Examiner takes the position that such a polynucleotide would be capable of hybridizing to SEQ IUD NO:2 or 5. Since the Office does

not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the polynucleotide encoding the protein of the prior art does not possess the same material structural and functional characteristics of the claimed polynucleotide). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

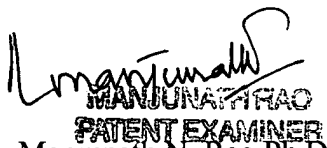
Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 3 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao Ph.D.
1/3/03